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CLINICAL RESEARCH

Treatment of atrial fibrillation by surgical epicardial ablation: Bipolar radiofrequency versus cryoablation

Traitement de la fibrillation atriale par cloisonnement épicaudique :
radiofréquence bipolaire versus cryoablation

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Summary Atrial fibrillation is the most frequent form of cardiac arrhythmia. Its surgical management has improved in recent years with major advances in our knowledge of the underlying pathogenic mechanisms. This has led to simpler therapeutic strategies such as epicardial ablation. The aim of this comparative experimental study was to evaluate the efficacy of this treatment, achieved with either bipolar radiofrequency or cryoablation.

Materials and methods. — Twelve sheep were used. After left thoracotomy, epicardial ablation of the junction between the left pulmonary veins and the left atrium was achieved by means of bipolar radiofrequency in group A ($n=6$) and by cryoablation in group B ($n=6$). Electrical stimulation thresholds were determined before and after ablation. Four weeks after ablation, sheep were killed for pathologic studies.

Results. — The mean stimulation threshold was 3.5 ± 0.6 mA before ablation and 15.6 ± 5.6 mA after ablation. The difference was significant in both groups, showing that effective conduction blockade was obtained with the two ablation methods. Histologic studies after radiofrequency and cryoablation showed limited coagulation necrosis and cellular rarefaction, respecting the supportive tissue.

Conclusions. — Both methods of surgical ablation by the epicardial route yielded effective electrical isolation of the pulmonary vein junction with the left atrium. This conduction blockade was due to limited coagulation necrosis with myocyte rarefaction, of similar extents in the two procedures. Standardization and refinement of this technique could extend the treatment

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MOTS CLÉS

Fibrillation atriale ;
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indications for atrial fibrillation associated with other cardiac disorders that require surgical treatment without opening the left atrium.

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Résumé La fibrillation atriale est le trouble du rythme cardiaque le plus fréquent. Son traitement chirurgical a bénéficié ces dernières années des progrès importants réalisés dans la connaissance de ses mécanismes pathogéniques. Ces progrès ont permis le développement de stratégies thérapeutiques plus simples, tel que le cloisonnement épicaudique. Nous avons entrepris cette étude expérimentale dans le but d'évaluer l'efficacité de ce traitement en comparant radiofréquence bipolaire et cryoablation.

Matériel et méthodes. — Douze brebis ont été opérées. Par thoracotomie gauche, des cloisonnements épicaudiques de la jonction veines pulmonaires gauches—oreillette gauche ont été effectués par radiofréquence bipolaire pour le groupe A ($n=6$) et par cryoablation pour le groupe B ($n=6$). Les seuils de stimulations électriques étaient déterminés avant et après ablation. Quatre semaines après ablation, les brebis étaient sacrifiées pour des études anatomopathologiques.

Résultats. — La moyenne des seuils de stimulation relevée avant ablation était de $3,5 \pm 0,6$ mA et passait à $15,6 \pm 5,6$ mA après ablation. La différence statistiquement significative pour les deux groupes témoignant d'un bloc de conduction efficace pour les deux méthodes d'ablation. Les résultats histologiques ont montré aussi bien après radiofréquence qu'après cryoablation des lésions limitées de nécrose de coagulation avec raréfaction cellulaire respectant le tissu de soutien.

Conclusions. — L'ablation chirurgicale par approche épicaudique permet d'obtenir un isolement électrique efficace de l'abouchement des veines pulmonaires à l'oreillette gauche dans les deux procédures d'ablation. Ce bloc de conduction est lié à des lésions limitées de nécrose de coagulation avec raréfaction myocytaire similaires dans les deux procédures. La standardisation et le raffinement de cette technique pourraient permettre d'étendre les indications de prise en charge de la fibrillation atriale associée à d'autres pathologies cardiaques dont la cure chirurgicale ne nécessite pas l'ouverture de l'oreillette gauche.

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Introduction

Atrial fibrillation is the most frequent cardiac arrhythmia. Its incidence is about 0.4% in the general population and increases significantly with age, reaching 5 to 6% after 60 years; it is generally associated with cardiac disorders and especially mitral valve disease [1,2]. This arrhythmia has seen a renewal of interest in recent years with improvements in our knowledge of the related morbidity and mortality, the electrophysiological mechanisms underlying its initiation and persistence, and its treatment [3,4]. Since the pioneering work of Cox, surgical treatment has taken an important place in the therapeutic arsenal. Despite sinus rhythm restoral in many patients, Cox surgery and its variants are technically difficult and carry a high risk of hemorrhage and postoperative conduction disorders due to the multiple incisions. Moreover, they significantly increase the ischemic period and myocardial ischemia [5]. Various modifications and conceptual improvements in Cox surgical techniques have been developed in recent years in order to avoid these pitfalls and to simplify the technique. In particular, there has been a move towards energy sources capable of reproducing the lines of Cox incisions (radiofrequency, cryotherapy, laser and microwaves), without the accompanying disadvantages. Whatever the energy source, deep transmural ablation lesions appear to be the main mechanical determinant of efficacy. This requires the use of high temperatures in the case of unipolar radiofrequency abla-

tion, but tissue resistance creates multidirectional energy flow [6] that can induce injury of the endocardium and neighboring tissues, including the esophagus. Cases of esophageal perforation, thromboembolic complications and pulmonary vein stenosis have been reported after unipolar radiofrequency ablation by the endocardial route [7,8]. To avoid these adverse effects, to improve efficacy and to simplify the technique, research has focused in recent years on the use of different energy sources and on the use of the epicardial route, which is theoretically less invasive with respect to the endocardium and neighboring organs. Moreover, the epicardial approach allows surgical treatment of atrial fibrillation to be performed during procedures that do not require left atriotomy, such as coronary and aortic surgery. The aim of this study was to examine, in an animal model, factors potentially influencing the efficacy of epicardial catheter ablation achieved by means of either bipolar radiofrequency or cryoablation. Efficacy was evaluated by measuring the degree of conduction blockade and the histologic lesions generated by ablation.

Materials and methods

The animal model used for this study was the sheep. All the animals came from the same breeder and were handled in keeping with Inserm guidelines (French Institute of Health and Medical Research). Twelve sheep with a mean weight of

35 kg (range 25–50 kg) were used. Premedication consisted of an intramuscular injection of 0.5% Vetranquil® (acepromazine) at a dose of 5 mg/kg. Induction was achieved with 1% Diprivan® (propofol) at a dose of 6 mg/kg via the jugular vein. After intubation with a no.7 tracheal tube, ventilation was ensured by a Siemens 900C® respirator (volume: 10 ml/kg; frequency: 24 per minute; FiO_2 : 60%). Anesthesia was maintained with a mixture of 60% oxygen and 1–2% Forene® (isoflurane). Antibiotics administration was started by intravenous injection of 1 g Cefacidal® (cephazolin sodium) and was continued for three days after surgery. Continuous electrocardiographic monitoring was performed throughout the operation. The animals were extubated after the operation.

Surgical technique, epicardial ablation and electrophysiological studies

The 12 sheep were divided into two groups. Group A underwent radiofrequency ablation ($n = 6$) and Group B underwent cryoablation ablation ($n = 6$). In both groups, the surgical approach consisted of left thoracotomy and opening of the pericardium behind the phrenic nerve, the left pulmonary veins being carefully dissected. Two temporary epicardial electrodes were placed upstream of the pulmonary vein junction and connected to an external pulse generator (Medtronic model 2380, high output external pulse generator). Stimulation thresholds were determined before and after ablation, using the following electrostimulation parameters: pulse duration: 0.5 ms; frequency: 250 ppm; energy: 1 to 40 milliamperes (mA). In group A, epicardial ablation was achieved with a bipolar radiofrequency clamp (Cobra bipolar system, Boston Scientific, USA). The pulmonary veins were clamped at the time of the procedure, at their junction with the left atrium. The radiofrequency parameters were the following:

- power: 40 W;
- temperature: 70 °C;
- duration: 20 s.

Tissue destruction by radiofrequency begins at 45 °C. Coagulation lesions and protein denaturation leads to a loss of cell function, without tissue incision, and starts at temperatures of 60–80 °C. The thickness of the lesions seems to be proportional to the duration, temperature and power setting, and varies between 2 and 3 mm for a temperature of 70 °C applied for 60 s, including direct and indirect lesions caused by heat diffusion.

In group B (6 sheep), ablation was achieved by cryoablation with a nitrogen monoxide (N_2O) cryosurgery unit (Frigitronics, Cooper Surgical, Connecticut, USA). The cryothermia probe was curved but rigid, allowing blood flow in the pulmonary veins to be reduced during the ablation procedure. The cryoablation parameters were as follows: temperature: –70 °C; duration: 2 min.

Animal sacrifice

Four weeks after surgical ablation, the animals were killed for pathological studies of the ablation site. Median sternotomy was used to avoid adhesions linked to the first thoracotomy. After dissection of the left pulmonary veins,

the stimulation thresholds were determined by placing two temporary electrodes upstream of the junction of the pulmonary veins and the left atrium. The animals were then killed by intravenous injection of Pentotal (thiopental sodium) and 2 g of potassium. The pulmonary veins and left atrium were removed, macroscopically examined, then immediately fixed in 10% formaldehyde for histological studies. The tissues were sliced into 3 μm -sections embedded in paraffin and stained with hematoxylin-eosin-saffron (HES) and orceine.

Statistical analysis

The results of the electrostimulation tests were compared using Student's *t* test. The difference in the mean stimulation thresholds was considered significant when $p < 0.05$.

Results

The only complication observed during an epicardial ablation procedure was a case of intractable ventricular fibrillation during the test of electrostimulation, at the end of a bipolar radiofrequency procedure. Postoperative complications consisted of a wall infection in a sheep sacrificed 15 days after the bipolar radiofrequency procedure and death of a sheep after a wool shearing session at the farm, 3 weeks after cryoablation.

Surgical technique

Surgical epicardial ablation by bipolar radiofrequency with the Cobra clamp was technically simpler than the cryoablation procedure. The Cobra bipolar clamp was easier to manipulate than the cryoablation probe and allowed the procedure to be performed in a single pass. Moreover, the bipolar radiofrequency system monitors the duration, temperature, power and tissue impedance, allowing the right energy level to be delivered to create transmural lesions, which was not the case with the cryoablation system.

Electrostimulation thresholds

The mean atrial stimulation threshold was 3.5 ± 0.6 mA before surgical ablation and 15.6 ± 5.6 mA after surgical ablation. The difference between the pre- and postablation thresholds was significant in both groups ($p < 0.05$). There was no significant difference in the stimulation thresholds between the two groups before or after surgical ablation. The mean threshold recorded just before sacrifice, that is 3 to 4 weeks after epicardial catheter ablation, was 13 ± 3.2 mA. There was no significant difference in either group between the stimulation thresholds measured after ablation and before sacrifice.

Histologic findings

Eleven of the 12 sheep were sacrificed for pathologic studies (one sheep died on the farm without autopsy).

Macroscopically, no thrombosis, perforation or stenotic lesions were seen in the pulmonary veins at the site of

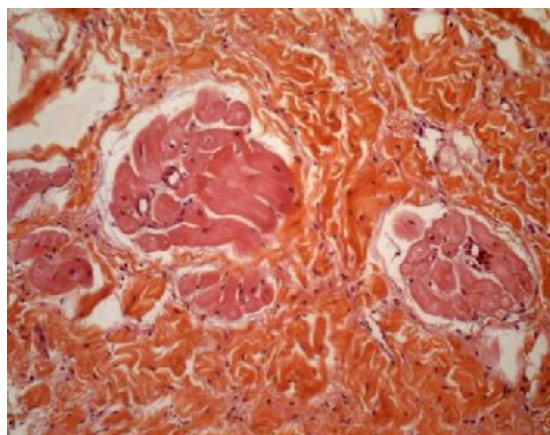


Figure 1. Histologic study of the left atrium showing myocyte rarefaction after bipolar radiofrequency (HES, $\times 200$).

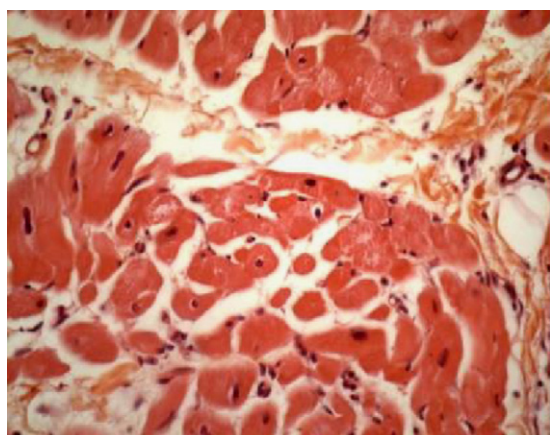


Figure 2. Foci of myocyte necrosis after radiofrequency at the junction between the left atrium and the pulmonary veins (HES, $\times 400$).

epicardial ablation. Histologic examination of the radiofrequency (Figs. 1 and 2) and cryoablation sites (Fig. 3) showed coagulation necrosis, rarified myocytes with picnotic nuclei and hypereosinophilia. This myocyte necrosis

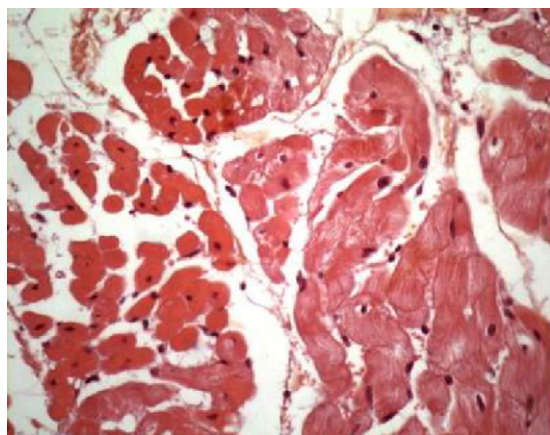


Figure 3. Necrosis and myocyte rarefaction in the wall of the left atrium after cryoablation (HES, $\times 400$).

was not accompanied by an inflammatory reaction. There were no signs of destruction of the supportive tissue (Figs. 1–3). No marked histological differences were noted between the two ablation methods.

Discussion

Treatment of isolated atrial fibrillation is mainly based on interventional cardiology approaches by the endocavitary route. Surgical treatment of atrial fibrillation is only warranted in patients who have an underlying cardiac disorder also necessitating surgery. This is why the two treatment approaches (endocardial vs epicardial) cannot be compared, their indications being different. Surgical isolation of the pulmonary veins can be achieved by the endocardial route (after opening the left atrium) or by the epicardial route. The main advantage of the epicardial method is that the pulmonary veins can be isolated without left atriotomy and on a beating heart, thus simplifying the surgical procedure and reducing the aortic clamp time and the risk of complications. This technical simplification may extend the indications of surgical management of atrial fibrillation to patients undergoing standard cardiac surgery (for example, treatment of atrial fibrillation associated with coronary or aortic surgery).

The main aim of this experimental study was to show the feasibility of pulmonary vein isolation by the epicardial route, using two different energy sources. This is why we chose to isolate the left pulmonary veins after left thoracotomy. Median sternotomy would be more suitable for complete isolation of the left and right pulmonary veins, but right or left thoracotomy seemed more appropriate in this experimental context, in terms of the surgical technique and postoperative recovery. By determining the stimulation thresholds before, immediately after and 1 month after epicardial catheter ablation, we were able to evaluate the efficacy of the two ablation procedures in terms of the degree of conduction blockade created at the pulmonary vein junction. The mean stimulation threshold rose from 3.5 ± 0.6 mA to 15.6 ± 5.6 mA after ablation and remained at 13 ± 3.2 mA at sacrifice, 1 month after ablation. The mean stimulation thresholds before and after ablation were significantly different ($p < 0.05$), showing effective conduction blockade between the two sides of the ablation site. There was no significant difference between the two ablation methods during stimulation tests. Stimulation tests have also been used elsewhere to assess electrical isolation of the atrial myocardium at the pulmonary vein junction with the left atrium [9,10]. According to Gillinov and MacCarthy [10], electrical isolation becomes effective when an electrode placed upstream of the ablation site is incapable of stimulating the atrium beyond an amplitude of 10 mA. In our study, effective conduction blockade was achieved after epicardial catheter ablation in all the operated sheep and with both methods. The stimulation thresholds were always at least 10 mA after ablation. It is therefore possible to electrically isolate the atrial myocardium at the junction between the left atrium and the pulmonary veins by using an epicardial approach. This part of the atrium is the main site at which atrial fibrillation arises and persists [4,11]. Other anatomical structures in the region of the right atrium (Marshall

ligament, interatrial septum, coronary sinus) can provoke supraventricular arrhythmias [4,12], which may explain the failure of some left monoatrial ablation procedures. In these cases, right atrial ablation by cardiac catheterization is the treatment of choice. It is also possible to combine the epicardial and endocardial approaches during the same operation. For example, permanent atrial fibrillation associated with mitral disease can be treated by the epicardial route, combined with endocardial lines created after opening the left atrium (lines between the pulmonary veins and the mitral annulus, left atrium) [13].

The main objective of the epicardial approach is to simplify the surgical ablation technique, based on a better knowledge of the pathogenic mechanisms of atrial fibrillation. Recently, the need to create lines of lesions between the left and right pulmonary veins or between the left pulmonary veins and the mitral annulus was challenged, especially in paroxysmic fibrillation [10,14]. Atrial ablation can thus be achieved by using a purely epicardial approach when the surgical procedure does not necessitate left atriotomy. Relative to endocardial ablation, the epicardial approach avoids the risks of esophageal perforation [7], reduces the risk of pulmonary vein stenosis and thromboembolic complications linked to endocardial trauma [8] and promotes atrial contractility after sinus rhythm restoral. Benussi et al. have shown that all patients who recover sinus rhythm after epicardial catheter ablation and mitral surgery also recover biatrial contractility 3 months after the operation [15]. When surgical ablation was performed by the endocardial route and with unipolar radiofrequency, only 67% of patients in sinus rhythm recovered biatrial electrical conduction [16]. This difference would appear to be linked to the more limited trauma of the atrial myocardium after epicardial ablation by bipolar radiofrequency [15]. The existence of an experimental model of atrial fibrillation would have allowed us to evaluate atrial contractility after sinus rhythm restoral by epicardial catheter ablation. This is the main limitation of our study which used "non pathological" atrial tissues, as in the case of atrial fibrillation.

The energy sources used for ablation can be divided into two main groups: those based on heating (radiofrequency, laser, and microwaves) and those based on freezing. We compared these two categories of energy source. Radiofrequency can be used in unipolar or bipolar mode. Bipolar radiofrequency circumscribes the delivered energy between two clamp inserts and thus avoids the bystander tissue damage associated with the multidirectional energy flow of unipolar radiofrequency ablation [6,9]. It would also allow the creation of circumferential and transmural lesions—essential for effective electrical isolation—on the beating heart. The histological existence of such transmural lesions is controversial, however [3,13], and it is difficult to show the complete nature of lesions created by ablation in clinical practice. Complete transmural lesions would nevertheless guarantee the efficacy of the procedure, but only histological studies can show the extent of the lesions. Even histologic results can be controversial. In our study, we observed the persistence of bridges of viable myocytes close to areas of coagulation necrosis and limited cell rarefaction. The apparent extent of the lesions also depends on where the sample is sectioned. Moreover, lesions cre-

ated by ablation gradually heal, likely explaining some cases of relapse after effective atrial ablation [3]. These scars lesions only become permanent after 6 months. Transmurality also depends on local conditions such as tissue texture, which is itself linked to the prior duration of the underlying mitral disease and to repeat surgery. In this latter case, the endocardial route appears to be more appropriate [3,15]. The Cobra device (Boston Scientific) used in our study, which monitors several parameters such as temperature, energy power and especially tissue conductance, allows the surgeon to overcome this problem by controlling the ablation conditions. According to Prasad et al. [9], tissue conductance can be used to determine when the lesion becomes transmural: when the target tissues are irreversibly damaged, the conductance between the clamp electrodes declines to a stable minimal value. The ablation can then be stopped, meaning that the energy delivered can be adjusted to the tissue texture. The use of this device therefore overcomes some of the problems of transmural, thanks to automatic regulation of conductance. The lesions thus induced are characterized by protein coagulation, myocyte degeneration and adipocyte loss. This technological refinement makes epicardial ablation by bipolar radiofrequency less empirical and more standardized than the cryoablation procedure we used. Indeed, the cryoablation probe provided no tissue feedback on the ablation parameters. However, cryothermia remains an interesting alternative to radiofrequency as the lesions tend to be more homogeneous, thus respecting the supportive tissue [17]. When performed by the epicardial route, cryoablation is also capable of creating effective electrical isolation [18,19]. Electrostimulation tests showed a similar degree of conduction blockade after cryoablation and bipolar radiofrequency in our study. There was no marked difference between the radiofrequency and cryoablation methods as regards the lesions at the site of ablation. These limited lesions consisted of coagulation necrosis, rarified myocytes with picnotic nuclei and hypereosinophilia. This type of lesion has been observed by other authors after surgical ablation by radiofrequency, cryothermia and even microwaves [9,20,21]. According to Manasse et al., tissue lesions created by cryothermia are characterized by edema due to osmotic effects of water crystallization [20]. We observed no significant edematous lesions after cryoablation on histologic examination. According to Kubota et al. [22], for cryolesions to be deep and transmural, blood flow through the pulmonary veins must be reduced by left chambers emptying during extracorporeal circulation. On the beating heart, as in our study, the traction around the pulmonary veins and the compression during cryoablation probe reduce blood flow and improve the efficiency of ablation. Epicardial catheter ablation is feasible in humans and the first promising results have already been published. A commercial epicardial system (Epicor, Saint Jude Medical) using high-frequency ultrasound was recently marketed and is increasingly used in clinical practice. This system uses a belt that goes round the pulmonary veins, passing behind the superior and inferior vena cava [23]. Possible complications of the epicardial method include damage to adjacent anatomical structures (vena cava, left atrium, circumflex artery). Cryoablation can deteriorate the phrenic nerve by cold diffusion.

Limitations of the study

Our model of isolated left pulmonary vein ablation is not intended as a treatment for atrial fibrillation in humans. This experimental model, limited to the left atrium, was designed to compare the feasibility and efficacy of two physical energy sources: cryogenics and radiofrequency. Our previous attempt to create a model of chronic atrial fibrillation by rapid electrostimulation of the atrium with a specific pacemaker (Itrel, Medtronic) was unsuccessful. The final histologic studies were performed at 1 month in our model, which was too early to show whether or not the lesions of ablation are reversible; similar studies should thus be conducted at time points beyond 6 months.

Conclusions

Surgical ablation by the epicardial approach yields effective conduction blockade around the pulmonary vein junction, whether bipolar radiofrequency or cryotherapy is used as the energy source. The type and extent of the ablation lesions were similar with the two energy sources. The lesions consist of limited coagulation necrosis with cell rarefaction and no marked insult to the supportive tissue. These methods are simple, effective and reproducible and could help to extend the indications of atrial fibrillation management to patients with other cardiac disorders necessitating cardiac surgery [24,25]. They also suggest that, in the near future, atrial fibrillation could be treated by using minimally invasive surgery and robotics [26], combined with left atrial appendage exclusion devices [27].

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